PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Robert HOFMEISTER *et al.*	Group Art Unit: 1643
Serial No.: 10/580,660	Examiner: Meera Natarajan
Filed: May 26, 2006	Atty. Dkt. No.: DEBE:066US
For: COMPOSITIONS COMPRISING POLYPEPTIDES	Confirmation No.: 1727

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this amendment is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

February 11, 2011
Date

Steven L. Highlander

DECLARATION OF THOMAS URBIG UNDER 37 C.F.R. §1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

I, Dr. Thomas Urbig, do declare that:

1. I am a citizen of Germany residing at Muenchener Strasse 27A, D-82131 Gauting. I am the Vice President of Process Sciences at Micromet AG, Munich, Germany. A copy of my *curriculum vitae* was previously submitted with my declaration dated July 1, 2009.

2. I have reviewed the above-captioned application and am familiar with its contents.

3. I would like to correct my previous declaration filed under 37 C.F.R. § 1.132 dated July 1, 2009 and submitted to the USPTO on July 23, 2009. The information provided in this referenced declaration was based on information that I was provided and that I believed to be true at the time that I signed this declaration. However, additional information was provided to me after I signed this declaration and, on the basis of this information, I wish to withdraw the statement made in the last sentence of paragraph 4, in which I stated, "As such, Dorken's compositions must be presumed to have much higher than 3% concentrations of multimeric proteins." To my knowledge and belief, the remainder of my previous declaration remains accurate.

4. I have also reviewed the grounds of rejection in the Office Action dated August 12, 2010.

5. The composition of the present invention contains a polypeptide comprising at least two antigen binding sites (human CD3 and human CD19) as claimed in SEQ ID NO:1, (hereinafter referred to as "Construct 1") and a citrate buffer containing lysine. But in early studies, Construct 1 in 1% human serum albumin ("HSA") in phosphate buffered saline ("PBS") (referenced as "CF" in the data presented herein) was used. However, due to stability problems in PBS and a strategic decision to eliminate HSA, our goal was to provide a formulation for Construct I that did not contain either HSA or PBS. In this regard, we determined that when Construct 1 was stored in PBS alone at +5°C and -80°C over a storage period of six months, it was determined that the dimer content increased over time. See attached Figure 1a. Increasing amounts of dimers of Construct 1 was an undesirable property, and thus, provided the impetus for the development of a more stable formulation. Further, CF contained the excipient, human serum

albumin, which pharmaceutical formulation scientists have been trying to eliminate from pharmaceutical formulations due to regulatory concerns over the risk of blood-borne contaminants, such as prions or viruses in these animal-derived products, and concerns over possible immunogenic responses in recipients. Thus, our additional goal was to eliminate HSA in the Construct 1 formulation.

6. To achieve this goal, citrate buffer was selected based on testing that showed that monomer recoveries of Construct 1 are more stable in citrate buffer at pH 5.5, 6.0 and 6.5 as measured by Size Exclusion Chromatography – High Performance Liquid Chromatography (SEC-HPLC) after incubation at 40°C for 7 days and 14 days as compared to monomer recoveries of Construct 1 contained in phosphate, histidine or succinate buffers in the pH ranges of 6.0 to 7.5. See the attached Figure 1b. Thus, based on this experimental data, I conclude that the presence of citrate buffer in a composition containing Construct 1 provides improved and unexpected stability of monomeric Construct 1 over 7 and 14 days of incubation as compared to Construct 1 in the other tested buffers.

6. With regard to the inclusion of lysine in the buffer of the claimed composition that contains Construct 1, the experimental data shows that lysine stabilizes Construct 1 monomers as measured by SEC-HPLC after incubation at 40°C for 7 days and 14 days as compared to Construct 1 incubated in the presence of other amino acids. CF (Construct 1 in 1% HSA in PBS) has been used as a reference. See the attached Figure 2. Thus, the presence of lysine in the buffer provides improved and unexpected stability of monomeric Construct 1 over 7 and 14 days of incubation as compared to the other tested amino acids.

7. Therefore, based on the data generated and provided in attached Figures 1a, 1b and 2, it is my opinion that a composition containing Construct 1 in combination with a buffer comprising citrate and lysine possesses the improved stability of the monomeric form of Construct 1 over time, which is an unexpected improvement over known buffers and other amino acids tested.

8. I also wish to clarify that Table 1 on page 26 of the present application does not disclose data of approximate percentages of monomers and dimers present in the specific single chain monoclonal antibodies produced by the method of the present invention. The data presented in Table 1 was obtained from the analysis of the harvested supernatant containing secreted polypeptide after the cells producing the polypeptide are separated from the culture media as disclosed in the first paragraph of Example 1, on page 19 of the above-identified application. A closer review of Example 3, beginning with the text on page 25 supports that bispecific antibodies were produced in CHO cells according to known methods, and then this supernatant was analyzed to determine the proportions of polypeptide in monomeric and dimeric form as determined by SDS-PAGE performed under reducing conditions, Western Blot and gel filtration. Table 1 was included in this application to show the percentage of dimers of the polypeptides that form when secreted by the cells and before purification according to the methods of the present invention. The sentence following Table 1 further supports my statements, and particularly, the phrase "spontaneously forms" further clarifies that the polypeptide that was tested was obtained directly from the CHO cells without purification:

> As can clearly be seen in Table 1, each bispecific single chain antibody with anti-human CD3 antigen binding specificity spontaneously forms significant amounts of multimeric (i.e., dimeric) species when left uncontrolled.

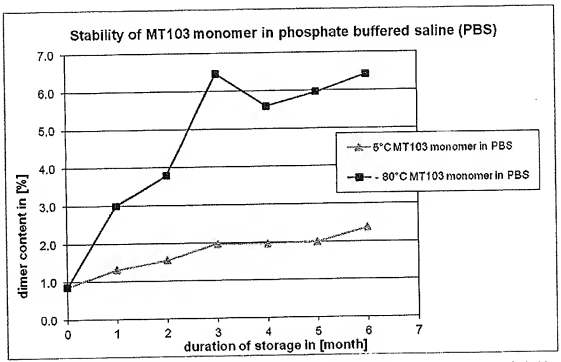
Therefore, I confirm that the percentage of dimers disclosed in Table 1 does not reflect the percentage of dimers present in polypeptide preparations purified according to the methods of the above-identified application, and therefore, does not appear to be relevant to the Examiner's lack of enablement rejection of the claimed composition.

9. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of title 18 of the United States Code.

11.02.2011
Date

Thomas Urbig, Ph.D.

FIGURE 1a



Stability of MT103 monomer in phosphate buffered saline (PBS) at +5°C(±3°C) and -80°C (±10°C) over a storage period of six month

MT103 monomer formulated in phosphate buffered saline (PBS) was stored over a period of six month at +5°C(±3°C) and -80°C (±10°C)

At each time point analytical HP-SEC (high performance size exclusion) was performed to determine the dimer content in the MT103 sample.

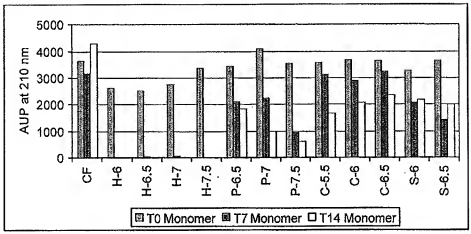
Results:

Starting with a content of 0.9% dimer at time point t=0 the dimer content is raised up to 2.4% after 6 month storage at +5°C(±3°C) indicating that MT103 is not stable under this conditions.

The data from the freezing at -80°C (±10°C) shows a dramatically increase of dimer to 6.4% dimer after 6 month of storage which implies an unstable formulation MT103 in PBS at this temperature.

FIGURE 1b

SEC-HPLC: Monomer recoveries of MT103 formulated in various buffers after incubation at 40°C for 7 days and 14 days.



AUP = Area under the Peak as measured at 210 nm

Tested Buffers Key

CF = MT103 in 1% human serum albumin in phosphate buffered saline

H = 20 mM Histidine buffer (pH 6, 6.5, 7, 7.5)

P = 20 mM Phosphate buffer (pH 6.5, 7, 7.5)

C = 20 mM Citrate buffer (pH 5.5, 6, 6.5)

S = 20 mM Succinate buffer (pH 6, 6.5)

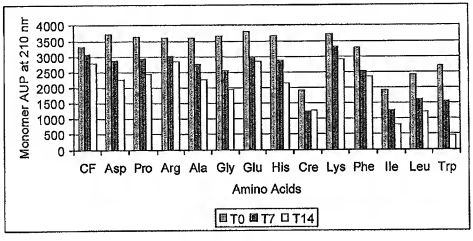
T0 = Monomer present on Day 0

T7 = Monomer present on Day 7

T14 = Monomer present on Day 14

FIGURE 2

Effect of amino acids, time and temperature (40°C) on monomer recoveries of MT103: SEC-HPLC



AUP = Area under the Peak as measured at 210 nm

Tested Amino Acid Key

CF = MT103 in 1% human serum albumin in phosphate buffered saline (no added amino acids)

Amino Acids Samples were prepared in 20mM Succinate buffer at pH 6, containing 50mM of each of the tested amino acids

T0 = Monomer present on Day 0

T7 = Monomer present on Day 7

T14 = Monomer present on Day 14